17. (New) The method according to Claim 13, wherein the metastases inhibited are lung metastases.

REMARKS

The claims have been amended to make explicit what has been implicit. The phrase "inhibiting cancer metastasis formation in a patient" has been modified to define the patient as having a primary cancerous tumor which is capable of metastasizing, but has not yet metastasized. Support for the language may be found throughout the specification and, in particular, at page 6, lines 8-9 and page 7, lines 1-5.

New claims 16 and 17 have been added to provide claims of diminishing scope.

The Patent Statutes, 35 USC §100, 101, Permit Patents to Issue For New Uses of Old Processes and Compositions of Matter

At the outset, one might ask why, since 1952, the patent statutes have specifically permitted the patenting of a new use for an "old process . . . composition of matter or material. (See 35 U.S.C. § 100(b)). Surely, an old process or composition of matter is already in the public domain. Yet, Congress deliberately chose to include as patentable subject matter the new use of an old process or composition of matter. One reason for this is the desire of our society to foster investigation of old processes and materials to find new uses therefor.

There is no evidence of record that prior to Applicants' work, those skilled in the art used doxorubicin to prevent metastasis in patients or even test animals. One must consider now many lives can be saved by knowing that a combination of doxorubicin and N-acetylcysteine may be used not only in a process for treating hematopoietic malignancies or advanced solid tumors as taught by *Doroshow et al.*, but also to treat tumors which are in their early stage and are subject to metastasization, in order to prevent the formation of metastases.

The Examiner should recognize that before a corporation can contemplate suggesting the use, commercially, of a combination of doxorubicin and N-acetylcysteine for the purpose of inhibiting tumor metastases, it is quite likely that the corporation selling the combination for that purpose would seek Food and Drug approval for the new use. Obtaining Food and Drug approval is an extremely expensive process. Accordingly, absent the grant of a patent, or some form of exclusivity, a corporation would be naturally reluctant to expend the funds necessary to develop the new use invention and obtain FDA approval since there will be no way of recouping the investment.

Accordingly, the Congress saw fit to enact legislation which permits obtaining patents for new uses of old processes and compositions because the grant of the patent serves to stimulate research and development and to bring valuable, potentially life saving, products to market.

Applicants' claims direct the invention specifically to the new use of inhibiting the formation of metastases in a patient having a primary cancerous tumor capable of metastasizing. Indeed, new Claim 17 is concerned with the new use of inhibiting lung metastases.

Doroshow & Freeman et al Do Not Teach or Make Obvious the Claimed New Use

Both the *Doroshow et al.* and *Freeman et al.* references of record have studied the effects of doxorubicin in models of primary malignancies. Such models are not really suitable as models for metastasis formation. Importantly, neither *Doroshow et al.* nor *Freeman et al.* noted or even mentioned prevention of metastases, the use that is claimed.

The *Freeman et al.* reference is directed to a study of the ability of N-acetylcysteine to antagonize the cardiotactic lethality of adriamycin (doxorubicin). It is described therein that adriamycin exhibits cardiotoxicity when administered. For example, in the paragraph

bridging pages 173-174 of *Freeman et al.*, the cardiotoxicity problems associated with adriamycin are spelled out in detail as follows:

> Many animals have been used to investigate the cardiomyopathy which can result from adriamycin chemotherapy. Single doses of adriamycin administered intravenously...or intraperitoneally...to mice produced a cardiomyopathy that was ultrastructurally similar to the changes seen in human cardiac tissue following adriamycin therapy.

Accordingly, the work done by *Freeman et al* with the combination of adriamycin and N-acetylcysteine was done to determine whether or not N-acetylcysteine prolongs the life of the patient by preventing heart problems. To this effect page 175 of the article states:

> We therefore propose that concurrent administration of the sulfahydryl compounds cysteamine or N-acetylcysteine may decrease the toxicity of adriamycin without decreasing its antitumor effect.

The Examiner has noted a particular passage at page 174, column 2, which states that at the lower dose used, the increase in life span was such that it suggested that the adriamycin-sulfahydryl compound combination potentiated the antineoplastic effect of adriamycin.

The Examiner relies on this statement, which says nothing about metastasis inhibition. The Examiner's attention is directed to Table 1 on page 172 of the *Freeman et al* article. This table sets forth the life span data which supports the previous statement. It is evident therein, that this potentiation effect is quite limited to the low dose of 1.5 mg/kg/day and that no potentiation was achieved when the dose was 2.5 mg/kg/day. Indeed, the data show that the life span was less when N-acetylcysteine was added to the treatment regimen at the higher dose. Accordingly, the Examiner's use of the life span data to suggest metastasis prevention is not warranted. All that the data really shows is that there is a significant difference in life span between the 1.5 mg/kg/day and 2.5 mg/kg/day adriamycin dosages (93 days versus 142 days). Indeed, it should be noted that *Freeman et al* attributed the increased life span which resulted at the lower dosage, to heart damage protection, not to prevention of metastasis.

Freeman et al specifically note that the "mechanism for the reduction in adriamycin induced toxicity is probably an enhancement of intracellular sulfahydryl levels and subsequent detoxification of adriamycin metabolites which are cardiotoxic". (Page 174, col. 2)

What is important, however, is that at no time did *Freeman et al.* suggest that the administration of a combination of doxorubicin and N-acetylcysteine could be used to prevent metastases of tumors as set forth in the claims herein. *Freeman et al.* simply doesn't suggest the new use.

There is nothing of record which shows that the *Freeman et al.* administration of the combination prevented metastases of tumors. Moreover, it is clear that even if the administration of the combination prevented metastases of tumors, *Freeman et al.* were unaware of it. It is well settled that that which may be inherent may not be known and if it is not known it cannot make something obvious. Indeed, the Supreme Court of the United States has advised that an accidental or unwitting duplication of an invention cannot constitute an anticipation. See *Tilghman v. Procter*, 102 U.S. 707 (1880); *Eibel Process, Co., v Minnesota and Ontario Paper Co.*, 261 U.S. 45 (1923). See also *In re Felton*, 179 USP 295,298 (CCPA 1973) in which the court relied on the *Tilghman* and *Eibel* process cases. Accordingly, the *Freeman et al.* work, which is directed to a type of tumor that is not a good model for metastases, cannot make the claimed subject matter obvious as set forth by the Examiner.

The Doroshow et al Teachings do not Make the Claimed Subject Matter Obvious

Claims 13-15 stand rejected under 35 USC §103 over *Doroshow et al.* As noted by the Examiner, *Doroshow et al.* teaches that "doxorubicin is an antineoplastic antibiotic that is now part of standard chemotherapeutic regimens for most hematopoietic malignancies as well as for advanced solid tumors of the breast, ovary, thyroid and bone".

The work done by *Doroshow et al* is simply not a good model for metastases. *Doroshow et al.* like *Freeman et al.* was concerned with doxorubicin cardiac toxicity and the use of N-acetylcysteine (NAC) to prevent the cardiac toxicity. Despite the fact that *Doroshow et al.* did considerable work and considerable sampling of tissue, *Doroshow et al.* does not suggest that the combination of N-acetylcysteine and doxorubicin has any effect on metastases. *Doroshow et al* attributes the enhanced survival of doxorubicin-treated mice that had received NAC to the ameliorating effect of NAC on the cardiac toxicity of doxorubicin. Additionally, *Doroshow et al* discusses the *Freeman et al* work in the paragraph bridging pages 1062-1063. *Doroshow et al* states:

> Freeman et al. (41) have recently found that NAC does not decrease the therapeutic activity of doxorubicin against the Erlich ascites carcinoma; when doxorubicin was administered using a multiple, low-dose treatment schedule in their study, NAC significantly enhanced the chemotherapeutic effect of doxorubicin. These results suggest that a major cytotoxic effect of doxorubicin on tumor cells may not be related to free radical formation; in that circumstance, NAC could have its predominant impact on the cardiac damage produced by doxorubicin rather than its antineoplastic activity.

It is clear that Doroshow did not interpret *Freeman et al.*'s results as indicating prevention of metastases. Rather, it appears that *Doroshow et al.* interpreted *Freeman et al*'s results as indicating that NAC works on cardiac damage produced by doxorubicin rather than its antineoplastic activity.

It is respectfully submitted that the references relied upon by the Examiner do not teach what is claimed by Applicants, namely the new use of administering a combination of doxorubicin and N-acetylcysteine to inhibit metastases formation.

It is respectfully submitted that the Court of Appeals of the Federal Circuit, like its predecessor the CCPA, recently reiterated the importance of permitting patents for a new use of an old process or composition of matter. In *Rapoport v. Dement*, 59 USPQ2d 1215 (Fed. Cir. 2001), the Court was faced with a claim directed to a "method for <u>treatment</u> of <u>sleep</u>

apneas using an azapirone compound. The Court held that this new use was patentable over a reference which taught use of the same azapirone compound for the treatment of "anxiety" which was a symptom of sleep apnea. Indeed, the reference even mentioned the possibility of administering the azapirone compound to patients suffering from sleep apnea but the Court noted that this was for the purpose of treating anxiety in such patients not for the purpose of treating the sleep apnea disorder itself. In other words, the Federal Circuit recognized the value of these new uses for old processes and compositions, the same value envisaged by Congress in permitting such patents. It may be that the Court recognized that possession of the patent right would provide the necessary incentive to do the work requisite for obtaining Food and Drug approval.

It should be noted that the *Rapaport* case in no "fluke" decided by an errant panel of the Federal Circuit. In *Rapaport*, the court reminded the PTO that the patent statute permitted such patents. The Federal Circuit's predecessor, the C.C.P.A., had similarly reminded the PTO in the case of *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978), where administration of a drug for weight loss was considered patentable over administration of the same drug to lower the acid content of the stomach. See also *In re Shetty*, 566 F.2d 81, 86, 195 USPQ 753, 252 (CCPA 1977) (Adamantine drug used for new use of appetite suppression).

It is respectfully submitted that the references relied on by the Examiner in the rejection do not suggest the claimed new process to which Applicants put the combination of N-acetylcysteine and doxorubicin. Absent that suggestion, a prima facie case of obviousness has not made out under the law.

The claims as amended include a claim which requires the doxorubicin (DOX) to be administered intravenously. The Examiner will note that in the specification, it is noted that a remarkable synergistic effect was noticed while administering both NAC and DOX and that

"this effect results to be particularly high when DOX is administered by intravenous route". (Page 2, lines 17-19.) New Claim 17 is directed to the inhibition of lung metastases. It is noted in the specification that DOX is particularly effective with regard to decreasing the number of lung metastases. See, in particular pages 9 and 10 which indicates that none of the 12 mice which received the combined treatment developed lung metastases. This was a significant drop in frequency of metastasis formation compared to the other groups tested. It is respectfully submitted that there is nothing in the references relied on by the Examiner which indicates the ability of the claim combination to inhibit the formation of lung metastases to the extent noted in the specification.

It is respectfully submitted that the claims of this application are nonobvious over the references relied on and warrant patent protection.

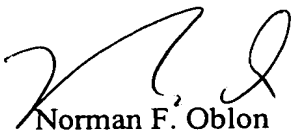
Upon entry of these amendments, Claims 13, 14, 15, 16 and 17 are pending in this application. Claim 13 is independent.

It is respectfully submitted that the claims of this Application are in condition for allowance and that an early indication of allowability is requested.

Should the Examiner believe that anything further is necessary in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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Attachment:
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MARKED-UP COPY OF AMENDMENTS

13. (Twice amended) A method for inhibiting [cancer metastasis] formation of a metastasis in a patient [in need thereof] having a primary cancerous tumor, which has not yet metastasized but is capable of metastasizing, the method comprising administering to [the] said patient N-acetyl-cysteine and doxorubicin together in a synergistic mixture or individually in amounts and within such a period as to act synergistically together to produce a cancer metastasis formation inhibiting effect.

15. (Amended) The method according to Claim 13, wherein the doxorubicin is administered in an amount between [1 and 50] 2 and 10 mg per dose.

16. (New) The method according to Claim 13, wherein said doxorubicin is administered intravenously.

17. (New) The method according to Claim 13, wherein the metastases inhibited are lung metastases.

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